

François Girardin · Michèle Siegenthaler
Philippe de Moerloose · Jules Desmeules

Rofecoxib interaction with oral anticoagulant acenocoumarol

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A 28-year-old female patient, known for a primary antiphospholipid syndrome, presented in 1996 multiple documented thrombosis of the portal, mesenteric, left internal iliac and left gonadic veins. Since then, oral contraception (desogestrel) was stopped and oral anticoagulation (acenocoumarol) initiated. Regular ambulatory international normalized ratio (INR) controls always remained in the expected therapeutic range (2.0–3.0) and required only few acenocoumarol dose adjustments.

Six years later, in April 2002, an ambulatory control revealed an INR value over 8.0 (checked twice). There was no history or clinical signs of hemorrhage. The only relevant anamnestic finding was right shoulder pain for which rofecoxib 50 mg/day had been taken orally for the prior 2 weeks. The withdrawal of rofecoxib and the administration of 4 mg vitamin K along with a temporary suspension of acenocoumarol brought the INR back into the therapeutic range. Acenocoumarol was then restarted and INR remained in the therapeutic range using previous doses. Genotyping for CYP2C9 indicated a wild type (*1/*1).

Rofecoxib, a highly selective inhibitor of cyclooxygenase-2, is extensively metabolized in the liver by reduction to dihydrorofecoxib and is not expected to have any clinically significant kinetic drug interaction with concomitant oral anticoagulants. However, an 8% increase in the mean INR is reported when rofecoxib is given together with warfarin [1]. Acenocoumarol and warfarin are administered as racemic mixtures, whose enantiomers undergo stereoselective hepatic metabolism by different

cytochromes P_{450} [2]. Absolute oral bioavailability of $R(+)$ -warfarin increases significantly by inhibition of CYP2C19 in contrast to its dynamically active $S(-)$ -warfarin, which is mainly metabolized by CYP2C9. Acenocoumarol (4-nitrowarfarin), widely used in some European countries, is chemically closely related to warfarin and also has stereoselective metabolic pathways [3]. In contrast to warfarin, the $R(+)$ -enantiomer of acenocoumarol is in clinical conditions more relevant. $R(+)$ -acenocoumarol undergoes relatively slow biotransformation by CYP2C9, CYP2C19 and CYP1A2, whereas $S(-)$ -acenocoumarol, albeit pharmacodynamically active, is promptly and extensively metabolized by CYP2C9. Polymorphism for CYP2C9 with poor metabolizer activity for $S(-)$ warfarin and both acenocoumarol enantiomers has been shown to result in overanticoagulation [4, 5]. Experimental evidences suggest that rofecoxib inhibits CYP1A2 and CYP2C19, which are implicated in the metabolism of the clinically most relevant isomer $R(+)$ -acenocoumarol [1]. Rofecoxib is therefore susceptible to increase significantly the exposure of $R(+)$ -acenocoumarol by decreasing the clearance, which clinically may lead to overanticoagulation.

Keeping in mind the above experimental evidence and considering the chronological relationship between rofecoxib exposure in this patient, the emergence of a high INR and the positive outcome after rofecoxib withdrawal, the imputability of a drug to drug interaction between rofecoxib and acenocoumarol remains probable.

Practitioners should therefore be particularly cautious when prescribing a high dosage of rofecoxib simultaneously with the oral anticoagulant acenocoumarol and closely monitor the INR when initiating or stopping rofecoxib therapy.

F. Girardin (✉) · J. Desmeules
Division of Clinical Pharmacology and Toxicology,
University Hospital Geneva, Micheli-du-Crest 24,
1205 Geneva, Switzerland
E-mail: francois.girardin@hcuge.ch
Fax: +41-22-3829934

M. Siegenthaler · P. de Moerloose
Hemostasis Unit, Division of Angiology and Haemostasis,
Department of Medicine, University Hospital Geneva,
1205 Geneva, Switzerland

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